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REVIEW

Small extracellular vesicles and liver diseases: From diagnosis to therapy

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Abstract

Extracellular vesicles (EVs), especially small EVs (sEVs) derived from liver cells, have been the focus of much attention in the normal physiology and pathogenesis of various diseases affecting the liver. sEVs are approximately 100 nm in size, enclosed within lipid bilayers, and are very stable. The lipids, proteins, and nucleic acids, including miRNAs, contained within these vesicles are known to play important roles in intercellular communication. This mini-review summarizes the application of sEVs. First, liver diseases and the related diagnostic markers are described, and the current active status of miRNA research in diagnosis of hepatocellular carcinoma (HCC) is reported. Second, the biodistribution and pharmacokinetics of sEVs are described, and the liver is highlighted as the organ with the highest accumulation of sEVs. Third, the relationship between sEVs and the pathogenesis of liver disorders is described with emphesis on the current active status of miRNA research in HCC recurrence and survival. Finally, the possibility of future therapy using sEVs from mesenchymal stem (stromal) cells for cirrhosis and other diseases is described.

Key Words: Small extracellular vesicles; Liver; cirrhosis; Hepatocellular carcinoma; Mesenchymal stem cells

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Core Tip: Extracellular vesicles (EVs), especially small EVs (sEVs) derived from liver cells, have been the focus of much attention in the normal physiology and pathogenesis of various diseases affecting the liver. sEVs are approximately 100 nm in size, enclosed within lipid bilayers, and are very stable. The proteins and nucleic acids, including miRNAs, contained within these vesicles are known to play important roles in intercellular communication. This mini-review summarizes the application of sEVs in the diagnosis of liver diseases, along with their distribution post administration, their role in pathogenesis, and their potential therapeutic effects in hepatic disorders.

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INTRODUCTION

The study of extracellular vesicles (EVs) is an active area of research. Recent evidence has established that these EVs are released not only by human cells, but also by plant, bacterial, and yeast cells[1]. EVs are sub-organellar entities that act as "cargo" carriers that transmit information between cells thus exerting a variety of effects on biological activities[1]. Since the vesicles released are unique to the cells that release them, they have been widely studied in diseases of various organs and systems, including diseases of the liver in the context of diagnosis, pathogenesis, and therapeutic applications[2-5]. In particular, small extracellular vesicles (sEVs; referred to as exosomes), with a particle size of approximately 100 nm, have garnered much attention in recent years[6-11].

Secretory vesicles were first described in the 1980s, and they have been referred to by a number of different names based on their size and cellular origin such as exosomes, ectosomes, microvesicles, shedding vesicles, apoptotic bodies, oncosomes, and prostasomes. The International Society for Extracellular Vesicles recommends the usage of extracellular vesicles as a general term for these entities. Small EVs (sEVs), or exosomes, are formed from early endosomes that are generated by endocytosis and subsequently mature into late endosomes[12,13].

The late endosomes expand to form intraluminal membrane vesicles, also referred to as multivesicular bodies (MVBs), which then fuse with the plasma membrane and are released into the extracellular space. Secreted vesicles with a diameter of 30–200 nm are called sEVs or exosomes, and they are known to encapsulate a content of proteins, mRNAs, and miRNAs within a membrane composed of cholesterol, sphingomyelin, ceramide, and lipid rafts[13]. Although these vesicles vary between cells, there are common markers that characterize most exosomes including membrane transport and fusion proteins (GTPases, annexins, flotillin, *etc.*), heat shock proteins (HSP60, HSP70, HSP90, *etc.*), tetraspanins (CD9, CD63, CD81, *etc.*), MVB formation and transport proteins (TSG101, ALIX, Annexins, *etc.*), and cytoskeletal proteins (actin, tubulin, *etc.*)[11-13]. sEVs can be have important applications in the diagnosis and treamtent of various diseases and malignancies, and their study can also contribute to the ellucidation of the pathogenesis of these disease. For example, the stable inclusion of drugs within the lipid bilayers of sEVs creates novel therapeutic drug delivery systems that can be implied in the treatment of different diseases[13] (Figure 1).

Investigations on EVs are rapidly moving beyond basic research to clinical trials, and the global market of the diagnostic and treatment strategies that use sEVs, although still in its infancy, is expected to progress rapidly. This paper reviews the role of sEVs in the context of diagnosis, pathogenesis, and treatment of liver diseases.

sEVs AND DIAGNOSIS OF LIVER DISEASES

Although different types of EVs were studied in the context of liver disorders, in this report we focus mainly on the role sEVs in the pathogenesis, diagnosis, and treatment of liver diseases. sEVs in particular have been analyzed in various chronic liver diseases such as non-alcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), viral hepatitis caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), cirrhosis, acute liver disease, and hepatocellular carcinoma (HCC); and in various specimens including blood, urine, bile, and ascitic fluid[5]. There are various techniques that were employed in the collection ofsEVs including ultracentrifugation, size exclusion chromatography, and methods utilizing precipitation kits and bead kits[14]. Details of sEV collection have been described in the minimal information for studies of extracellular vesicles guidelines 2018 (MISEV2018)[13]. After their collection, sEVs have been evaluated by western blotting, ELISA, flow cytometry, and nano

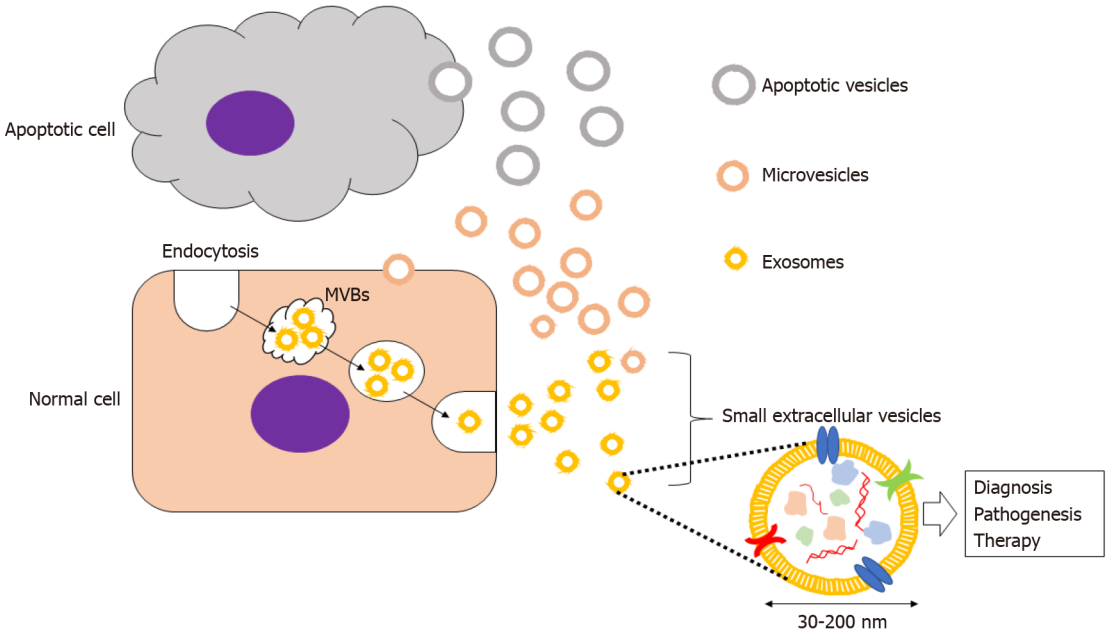

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Figure 1 Extracellular vesicles and liver diseases. Extracellular vesicles (EVs) include apoptotic vesicles, microvesicles, and exosomes. Small EVs (sEVs), or exosomes, are formed from early endosomes that are generated by endocytosis and subsequently mature into late endosomes. The late endosomes expand to form intraluminal membrane vesicles, also referred to as multivesicular bodies, which fuse with the plasma membrane and are released into extracellular space. These sEVs, or exosomes, are analyzed for diagnosis, pathogenesis, and therapy of various diseases including liver diseases.

tracking analysis to study the expression of common sEVs proteins, such as tetraspanins, and to identify markers including lipids, proteins, and nucleic acids, such as miRNAs and lincRNAs. Although the aforementioned studies are in the pre-clinical stage, they are expected to yield specific markers that can aid the processes of early and definitive diagnosis, treatment, and follow-up of liver diseases, in addition to helping in the ellucidation of the pathophysiology governing many of these liver disorders. Table 1[15-71] summarizes the various liver diseases and their related sEVs diagnostic markers. The bulk of the studies reported on miRNAs as sEVs diagnostic biomarkers of liver diseases which may be due to the ease of evaluating them using qRT-PCR. Markers of HCC have been the most frequently analyzed, and diseases such as NASH and ALD have received the most attention in recent years. Extracting sEVs produced by target cells and using them as markers of disease can contribute greatly to the field of diagnosis and treatment of liver disorders. However, we believe that there are some limitations and challenges to be acknowledged and addressed in the future, such as the efficient collection of target sEVs, recognition of target molecules (*e.g.*, protein miRNA), cost, and high reproducibility.

BIODISTRIBUTION AND PHARMACOKINETICS OF sEVs

Numerous studies have demonstrated the importance of the liver in the biodistribution and pharmacokinetics of sEVs. This has been accomplished by employing techniques such as lipophilic fluorescent and luminescent, radio-labeling, and magnetic resonance imaging. Studies have conclusively shown that post systemic administration of sEVs, these vesicles are cleared from the bloodstream within a few minutes of their half-life *via* phagocytosis by macrophages and neutrophils[72]. While they disappear from the blood, they have been reported to persist longer within organs, with the largest accumulation occurring in the liver. This accumulation peaks in the liver and kidneys approximately 1 h post administration, which is earlier than that in the lungs where maximal accumulation is achieved 2–12 h post administration. It has been shown that high concentrations of sEVs can be maintained in the liver for about 12-24 h, although there have been contradictory reports about this[72,73]. Some studies suggest that the macrophages primarily take up scaffold in the liver, while others report that hepatocytes and other cells also do the same. The abundant expression of scavenger receptors in macrophages is thought to play a crucial role in this process[73]. Additionally, phosphatidyl serine (PS) has been found to easily accumulate in the liver unlike the phosphatidylcholine-rich lipids[73]. Hoshino *et al*[74] have demonstrated the importance of integrins by showing that integrin αvβ5 in sEVs is essential for its accumulation in macrophages. However, results from these studies must be interpreted with caution since most of them employed the technique of labeling lipid bilayers, which may have resulted in the

Table 1 Diagnostic small extracellular vesicles markers in relation to liver diseases

Diseases	Types of molecules	Markers	Refs.
HCC	Protein	Aminopeptidase N, Galectin-3-binding protein, SMAD, ANGPT2, 14-3-3 ζ, β-catenin, P120-catenin, EPCAM	[15–21]
	RNA	miR-21, miR-21, -96, miR-122, miR-18a, -221, -222, -224, miR-10b-5p, -215-5p, miR-101, -106b, 12, -195, miR-519d, -595, -939, miR-19b,-92, miR-125, miR-9-3, miR-122, 148a, -1246, miR-122, miR-93, miR 144-3p, -21-5p, miR210, miR-638, miR-665, miR-774, miR-1262, miR-320d, miR-23a/b, miR-45-1a, miR-224, miR-21, -10b, miR-122, -125b, -145, -192, -194, 29a, 17-5p, -106a, miR-26a, -29c, -21, lncRNA Jpx, lncRNA FAL1, lncRNA-RP11-513I15.6, mRNA RAB11A, miR-1262, lncRNA HEIH, lncRNA LINC00161, lnc RNA HULC, AFP mRNA	[22–50]
HBV	miRNA	miR-21-5p	[33]
HCV	RNA	HCV-RNA, miR-122-5p, -222-3p, -146-5p, -150-5p, -30c-5p, -378a-3p, -20a-5p,	[51–53]
NAFLD/NASH	Protein	ITGβ1, CD68	[54,55]
	RNA	miR-192-5p	[56]
	Lipid	ceramides and sphingosin 1-phosphate	[57]
ALD	Protein	ASGR2 and CYP2E1, CD163, 206, ASGPR, CD40L, CK18, Glutathione synthetase	[55,58–62]
	RNA	miR-122, -155, miR-Let-7f, 29a, -340, miR-122, let7f, -21, -29a, -146a, miR-192-5p, miR-192, -30a	[56,63–66]
	Lipid	Sphingosin 1-phosphate	[67]
Cirrhosis	Protein	CD163, 206, PDGFRβ, urinary maltase and glucoamylase (for AKI during cirrhosis)	[59,68–70]
	RNA	miR-19a, -19b, -92, 17a, -20a	[27]
ALI	Protein	Apolipoprotein A-1, Argininosuccinate synthase-1	[62]
	RNA	Gnb21 mRNA,	[71]

HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; ALD: Alcoholic liver disease; ALI: Acute liver injury; RNA: Ribonucleic acid; SMAD: Suppressor of Mothers against Decapentaplegic; ANGPT: Angiopoietin; EPCAM: Epithelial cell adhesion molecule; lnc: Long non-coding; FAL1: Focally amplified lncRNA on chromosome 1; HEIH: High expression in hepatocellular carcinoma; HULC: Highly up-regulated in liver cancer; LINC: Long intergenic noncoding; AFP: α-fetoprotein; ITG: Integrin; CD: Cluster of differentiation; ASGR: Asialoglycoprotein receptor; CYP: Cytochrome P450; ASGPR: Asialoglycoprotein receptor; CK: Cytokeratin; PDGFR: Platelet-derived growth factor; AKI: Acute kidney injury; Gnb: Guanine nucleotide binding protein.

visualization of cells that ingested phospholipids rather than the sEVs. Given their miniscule size, sEVs by themselves have never been directly visualized in isolation. Furthermore, the majority of these reports have made observations under conditions of normal physiology, so it is possible that the biodistribution and pharmacokinetics of sEVs in pathological conditions may be significantly different.

sEVs AND LIVER PATHOGENESIS

Many reports described the implication of sEVs in various aspects of the pathogenisis of liver diseases. These entities are highly stable *in vivo* and play an important role in the communication between both neighboring and distant cells. Table 2[75-99] summarizes the different sEV markers that have been linked to certain processes of liver pathogenesis.

sEVs exert their effect on inter-cellular communication between neighboring cells *via* the peri-sinusoidal space. For instance, it has been reported that sEVs secreted by HCV-infected hepatocytes exert an effect on hepatic stellate cells (HSCs) driving hepatic fibrosis[100]. Additionally, as shown in Table 2, sEVs produced by hepatocellular carcinoma (HCC) have a profound effect on the surrounding environment. This effect is mediated by the modulation of the immune system by sEVs that have an inhibitory effect on macrophages, monocytes, NK cells, B cells, and T cells[101]. These vesicles can also promote HSC and the transformation of fibroblasts to cancer-associated fibroblasts (CAFs), promote migration of hepatocellular carcinoma cells in the vicinity, act on vascular endothelial cells to promote angiogenesis, and induce drug resistance in surrounding cancer cells[101]. Additionally, sEVs released from hepatocytes are believed to function as drivers of inflammation and state formation in inflammatory cells such as macrophages in NASH[102].

Table 2 Small extracellular vesicles markers in relation to liver pathogenesis

Pathophysiology	Types of molecules	Markers	Refs.
NASH inflammation and fibrosis	miRNA	miR-122, -192	[75]
NASH fibrosis	miRNA	miR-122	[76]
ALD outcome	protein	ASGR2 and CYP2E1	[58]
HBV fibrosis	miRNA	miR-150, -192, -200b, -91a	[77]
HCV treatment response	miRNA	miR-122, -199a, miR-122, miR-122-5p, -222-3p, -146-5p, -150-5p, -30c-5p, -378a-3p, -20a-5p	[53,78,79]
HCV fibrosis	protein	CD81	[80]
	miRNA	Let-7s, miR-122, -150, -192, 200b, 92a, miR-19a	[77,81]
HCC recurrence	protein	SMAD3, CASC9	[16,82]
	RNA	miR-718, miR-125, miR-21, miR-103, miR1247-3p, miR-92b, miR-21 and lncRNA-ATB, miR-21, -10b, miR-215-5p, miR-155, mRNA RAB11A, miR-211-3p, -6826-3p, -1236-3p, 4448	[25,26,36,42,83–90]
HCC survival	RNA	miR-125, miR-21, miR-103, miR-22a-3p, miR-335, miR-25-5p, miR-320a-PBX3, miR-718, miR-210, miR-122, miR-93, miR-21, -96, -122, miR-1247-3p, miR-638, miR-665, miR-21 and lncRNA-ATB, miR-30d, -140, miR-106a, miR-224, miR-320d, long non-coding RNA (ENSG00000258332.1 and LINC00635), hnRNPH1, circPTGR1, circRNA-100, -338, circ DB	[18,23,31,32,34,36,38,41,43,82–86,88,91–99]

NASH: Nonalcoholic steatohepatitis; ALD: Alcoholic liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; RNA: Ribonucleic acid; ASGR: Asialoglycoprotein receptor; CYP: Cytochrome P450; CD: Cluster of differentiation; SMAD: Suppressor of Mothers against Decapentaplegic; CASC: Cancer Susceptibility; PBX: Pre-B cell leukemia homeobox; lnc: long non-coding; ATB: Activated By TGF-Beta; ENSG: Ensembl Gene ID; LINC: Long intergenic noncoding; RNPH: Ribonucleoprotein H; PTGR: Prostaglandin Reductase; DB: Deubiquitination.

It has been also reported that these vesicles drive the pathogenesis of disease through an effect on distant cells. This is exemplified by the crosstalk between the sEVs produced by adipocytes and those produced by hepatocellular carcinoma cells, which contributes to cell proliferation, angiogenesis, invasion, epithelial-mesenchymal transition, and the creation of a favorable environment for metastasis [103]. Recent reports have also demonstrated that microbiota-derived EVs in the intestine affect other organs and tissues in the body, including the liver, heart, brain, kidney, lung, and adipose tissue[104]. Though there have been some studies describing the effects of sEVs on various cells in the body, it is still unclear how these sEVs that are produced by specific cells selectively reach their target cells. Consequently, further analysis from a broader perspective is essential to describe the specificities and dynamics of this interaction between sEVs and their target cells.

sEVs AND THE TREATMENT OF LIVER DISEASES

To date, there have been no reports or ongoing trials on the application of sEVs in the treatment of liver diseases. This scarcity might be attributed to the fact that there are still many unknowns regarding the effects of sEVs on liver disease, but further mechanistic analysis in the future may lead to the development of new therapies. However, the potential of sEVs as anti-fibrotic and anti-cancer therapeutic agents needs to be explored. In the case of anti-fibrotic therapy, sEVs may be the most convenient therapeutic agents that target macrophages on account of their massive accumulation in these cells within the liver[5,105]. Furthermore, Mesenchymal stem (stromal) cells (MSCs) have been investigated for their anti-fibrotic properties due to their ability to suppress fibrogenesis by reducing the inflammatory responses of inflammatory cells and by inducing fibrolysis *via* their effect on macrophages and matrix metalloproteinases[106].

Basic research has recently revealed that sEVs secreted by MSCs transmit information to macrophages. Additionally, the potency of these sEVs has been enhanced by pre-conditioning the MSCs with IFN-γ to augment their therapeutic effects in a mouse model of liver cirrhosis[105]. In view of this, it might be possible to create and evaluate a therapeutic strategy that employs sEVs obtained from pre-conditioned or modified MSCs to transmit information to macrophages and exert anti-fibrotic effects suppressing fibrogenesis. Although such attempts have been made, the production of sEVs from preconditioned/modified MSCs has not yet been successful due to regulatory concerns, lack of appropriate quality control, and difficulties associated with mass purification.

Warnecke *et al*[107] reported a first-in-human case study that utilized MSC-EVs derived from umbilical cord tissues to reduce inflammation during cochlear implantation. Briefly, the authors obtained 1.03 × 10^{11} particles/mL of EVs with a diameter range of 110–130 nm, as measured by nanoparticle tracking analysis, *via* a combination of tangential flow filtration (TFF) and diafiltration techniques post culture. This showed that MSCs-derived exosomes may find successful application in clinical use. Furthermore, improvements in the methods that can reduce the quantity of exosomes needed for efficient treatment will further expedite their use in clinical scenarios[107].

The development of cancer therapies that employ sEVs are also theoretically possible, such as those that aim to suppress sEVs derived from cancer cells. Mendt *et al*[108] have developed a therapeutic strategy for pancreatic cancer using sEVs that is currently under clinical trials. Their study involved the optimization of iExosomes to enable them to deliver higher concentrations of sEVs to pancreatic cancers *via* a two-pronged strategy. This includes the selection of CD47 that protects exosomes from phagocytosis by macrophages and engineering exosomes to carry siRNA or shRNA specifically targeted against the oncogenic KRASG12D, the key driver of pancreatic cancer. The study also reported the feasibility of large-scale production of clinical grade iExosomes by a bioreactor-based methodology[108, 109]. Therefore, sEVs have a promising potential in anti-fibrotic and anti-cancer therapy, and their applications may be expanded by developing techniques that efficiently load therapy enhancing substances, aid their incorporation into target cells, and improve high-throughput collection methodologies.

CONCLUSION

In summary, small extracellular vesicles (sEVs) have a promising potential in the diagnosis and treatment of liver diseases. The challenge in the therapeutic uses of sEVs is that it is not easy to harvest large amout of sEVs for human systemic therapy. However, the collection of sEVs can be greatly enhanced by pre-conditioning or modifying the source cells, thereby greatly expanding their possible applications. Furthermore, the potential for using EVs in therapy may be enhanced by utilizing larger EVs in addition to sEVs. These vesicles can potentially be harvested from cell sources other than mesenchymal stem cells (MSCs), such as induced pluripotent stem cells (iPS cells). In addition, with using these larger EVs there are fewer risk of embolization especially to the lungs after the administration. Consequently, in spite of issues with future regulatory trends and establishment of manufacturing processes, sEVs remain a promising therapeutic option for liver ailments.

FOOTNOTES

Author contributions: Tsuchiya A collected and analyzed the data and wrote the manuscript; Natsui K, Ishii Y, Koseki Y, Takeda N, Tomiyoshi K, Yamazaki F, and Yoshida Y collected the data; Terai S supervised the manuscript; and All authors reviewed the manuscript.

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